

FENTANYL - fentanyl patch

Actavis South Atlantic LLC

Full Prescribing Information

FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

BOXED WARNING

Fentanyl transdermal system contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (fentanyl transdermal system) may be a particular target for abuse and diversion.

Fentanyl transdermal system is indicated for management of persistent, moderate to severe chronic pain that:

- requires continuous, around-the-clock opioid administration for an extended period of time, and
- cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids

Fentanyl transdermal system should **ONLY** be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to fentanyl transdermal system 25 mcg/hr. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal system is contraindicated:

- in patients who are not opioid-tolerant
- in the management of acute pain or in patients who require opioid analgesia for a short period of time
- in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)
- in the management of mild pain
- in the management of intermittent pain [e.g., use on an as needed basis (prn)]

(See CONTRAINDICATIONS for further information.)

Since the peak fentanyl levels occur between 24 and 72 hours of treatment, prescribers should be aware that serious or life-threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period.

The concomitant use of fentanyl transdermal system with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression.

Patients receiving fentanyl transdermal system and potent CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted. (See CLINICAL PHARMACOLOGY - Drug Interactions, WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION for further information.)

The safety of fentanyl transdermal system has not been established in children under 2 years of age. Fentanyl transdermal system should be administered to children only if they are opioid-tolerant and age 2 years or older (see PRECAUTIONS - Pediatric Use).

Fentanyl transdermal system is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the fentanyl transdermal system dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of fentanyl transdermal system, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

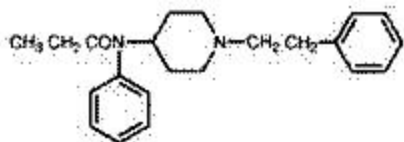
Fentanyl transdermal system can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing fentanyl transdermal system in situations where the health care professional is concerned about increased risk of misuse, abuse or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

Fentanyl transdermal systems are intended for transdermal use (on intact skin) only. Using damaged or cut fentanyl transdermal systems can lead to the rapid release of the contents of the fentanyl transdermal system and absorption of a potentially fatal dose of fentanyl.

DESCRIPTION

Fentanyl transdermal system is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. The chemical name is N-Phenyl-N-(1-(2-phenylethyl)-4-piperidinyl) propanamide. The structural formula is:



The molecular weight of fentanyl base is 336.5, and the molecular formula is $C_{22}H_{28}N_2O$. The n-octanol:water partition coefficient is 860:1. The pKa is 8.4.

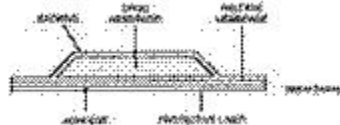
System Components and Structure

The amount of fentanyl released from each system per hour is proportional to the surface area (25 mcg/hr per 10 cm²). The composition per unit area of all system sizes is identical. Each system also contains 0.1 mL of alcohol USP per 10 cm².

Dose* (mcg/hr)	Size (cm ²)	Fentanyl Content (mg)
25	10	2.5
50	20	5
75	30	7.5
100	40	10

*Nominal delivery rate per hour

Fentanyl transdermal system is a rectangular transparent unit comprising a protective liner and four functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are: 1) a backing layer of polyester film; 2) a drug reservoir of fentanyl and alcohol USP gelled with hydroxyethyl cellulose; 3) an ethylene-vinyl acetate copolymer membrane that controls the rate of fentanyl delivery to the skin surface; and 4) a fentanyl containing silicone adhesive. Before use, a protective liner covering the adhesive layer is removed and discarded.



The active component of the system is fentanyl. The remaining components are pharmacologically inactive. Less than 0.2 mL of alcohol is also released from the system during use.

Do not cut or damage fentanyl transdermal system. If the fentanyl transdermal system is cut or damaged, controlled drug delivery will not be possible, which can lead to the rapid release and absorption of a potentially fatal dose of fentanyl.

CLINICAL PHARMACOLOGY

Pharmacology

Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system.

In addition to analgesia, alterations in mood, euphoria, dysphoria, and drowsiness commonly occur. Fentanyl depresses the respiratory centers, depresses the cough reflex, and constricts the pupils. Analgesic blood levels of fentanyl may cause nausea and vomiting directly by stimulating the chemoreceptor trigger zone, but nausea and vomiting are significantly more common in ambulatory than in recumbent patients, as is postural syncope.

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening rather than relief of pain.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination. At therapeutic dosages, fentanyl usually does not exert major effects on the cardiovascular system. However, some patients may exhibit orthostatic hypotension and fainting.

Histamine assays and skin wheal testing in clinical studies indicate that clinically significant histamine release rarely occurs with fentanyl administration. Clinical assays show no clinically significant histamine release in dosages up to 50 mcg/kg.

Pharmacokinetics(see graph and tables)

Fentanyl transdermal system releases fentanyl from the reservoir at a nearly constant amount per unit time. The concentration gradient existing between the saturated solution of drug in the reservoir and the lower concentration in the skin drives drug release. Fentanyl moves in the direction of the lower concentration at a rate determined by the copolymer release membrane and the diffusion

of fentanyl through the skin layers. While the actual rate of fentanyl delivery to the skin varies over the 72-hour application period, each system is labeled with a nominal flux which represents the average amount of drug delivered to the systemic circulation per hour across average skin.

While there is variation in dose delivered among patients, the nominal flux of the systems (12.5, 25, 50, 75, and 100 mcg of fentanyl per hour) is sufficiently accurate as to allow individual titration of dosage for a given patient. The small amount of alcohol which has been incorporated into the system enhances the rate of drug flux through the rate-limiting copolymer membrane and increases the permeability of the skin to fentanyl.

Following fentanyl transdermal system application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. Serum fentanyl concentrations increase gradually following initial fentanyl transdermal system application, generally leveling off between 12 and 24 hours and remaining relatively constant, with some fluctuation, for the remainder of the 72-hour application period. Peak serum concentrations of fentanyl generally occurred between 24 and 72 hours after initial application (see Table A). Serum fentanyl concentrations achieved are proportional to the fentanyl transdermal system delivery rate. With continuous use, serum fentanyl concentrations continue to rise for the first few system applications. After several sequential 72-hour applications, patients reach and maintain a steady state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl (see graph and Table B).

After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 17 (range 13 to 22) hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life is approximately 7 (range 3 to 12) hours.

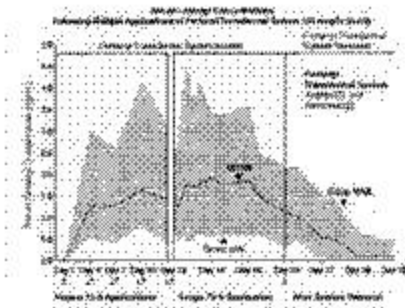


TABLE A FENTANYL PHARMACOKINETIC PARAMETERS FOLLOWING FIRST 72-HOUR APPLICATION OF FENTANYL TRANSDERMAL SYSTEM

	Mean (SD) Time to Maximal Concentration T _{max} (hr)	Mean (SD) Maximal Concentration C _{max} (ng/mL)
Fentanyl Transdermal System 12.5 mcg/hr	27.5 (9.6)	0.3 (0.2)
Fentanyl Transdermal System 25 mcg/hr	38.1 (18.0)	0.6 (0.3)
Fentanyl Transdermal System 50 mcg/hr	34.8 (15.4)	1.4 (0.5)
Fentanyl Transdermal System 75 mcg/hr	33.5 (14.5)	1.7 (0.7)
Fentanyl Transdermal System 100 mcg/hr	36.8 (15.7)	2.5 (1.2)

NOTE: After system removal there is continued systemic absorption from residual fentanyl in the skin so that serum concentrations fall 50%, on average, in 17 hours.

TABLE B RANGE OF PHARMACOKINETIC PARAMETERS OF INTRAVENOUS FENTANYL IN PATIENTS

	Clearance (L/hr) Range [70 kg]	Volume of Distribution V _{ss} (L/kg) Range	Half-Life t _{1/2} (hr) Range
Surgical Patients	27 - 75	3 - 8	3 - 12
Hepatically Impaired Patients	3 - 80 ⁺	0.8 - 8 ⁺	4 - 12 ⁺
Renally Impaired Patients	30 - 78	—	—

⁺Estimated

NOTE: Information on volume of distribution and half-life not available for renally impaired patients. Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. Fentanyl accumulates in the skeletal muscle and fat and is released slowly into the blood. The average volume of distribution for fentanyl is 6 L/kg (range 3 to 8; N=8).

In 1.5 to 5 year old, non-opioid-tolerant pediatric patients, the fentanyl plasma concentrations were approximately twice as high as that of adult patients. In older pediatric age patients, the pharmacokinetic parameters were similar to that of adults. However, these findings have been taken into consideration in determining the dosing recommendations for opioid-tolerant pediatric patients (2 years of age and older). For pediatric dosing information, refer to DOSAGE AND ADMINISTRATION section.

The kinetics of fentanyl in geriatric patients have not been well studied, but in geriatric patients the clearance of IV fentanyl may be reduced and the terminal half-life greatly prolonged (see PRECAUTIONS).

Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system. In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites. Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13 and 21%. Skin does not appear to metabolize fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

Drug Interactions

The interaction between ritonavir and fentanyl was investigated in eleven healthy volunteers in a randomized crossover study.

Subjects received oral ritonavir or placebo for 3 days. The ritonavir dose was 200 mg tid on Day 1 and 300 mg tid on Day 2 followed by one morning dose of 300 mg on Day 3. On Day 2, fentanyl was given as a single IV dose at 5 mcg/kg two hours after the afternoon dose of oral ritonavir or placebo. Naloxone was administered to counteract the side effects of fentanyl. The results suggested that ritonavir might decrease the clearance of fentanyl by 67%, resulting in a 174% (range 52% to 420%) increase in fentanyl AUC_{0-∞}. Coadministration of ritonavir in patients receiving fentanyl transdermal system has not been studied; however, an increase in fentanyl AUC is expected. (See BOX WARNING, WARNINGS, DOSAGE AND ADMINISTRATION and PRECAUTIONS.)

Pharmacodynamics

Ventilatory Effects

Because of the risk for serious or life-threatening hypoventilation, fentanyl transdermal system is CONTRAINDICATED in the treatment of post-operative and acute pain and in patients who are not opioid-tolerant. In clinical trials of 357 patients with acute pain treated with fentanyl transdermal system, 13 patients experienced hypoventilation. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO₂ greater than 55 mm Hg. In these studies, the incidence of hypoventilation was higher in nontolerant women (10) than in men (3) and in patients weighing less than 63 kg (9 of 13). Although patients with impaired respiration were not common in the trials, they had higher rates of hypoventilation. In addition, post-marketing reports have been received that describe opioid-naïve post-operative patients who have experienced clinically significant hypoventilation and death with fentanyl transdermal system.

While most patients using fentanyl transdermal system chronically develop tolerance to fentanyl induced hypoventilation, episodes of slowed respirations may occur at any time during therapy. Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations, especially for patients who have an underlying pulmonary condition or who receive usual doses of opioids or other CNS drugs associated with hypoventilation in addition to fentanyl transdermal system. The use of fentanyl transdermal system is contraindicated in patients who are not tolerant to opioid therapy. The use of fentanyl transdermal system should be monitored by clinical evaluation, especially within the initial 24 to 72 hours when serum concentrations from the initial patch will peak, and following increases in dosage. Fentanyl transdermal system should be administered to children only if they are opioid-tolerant and 2 years of age or older.

See BOX WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE for additional information on hypoventilation.

Cardiovascular Effects

Fentanyl may infrequently produce bradycardia. The incidence of bradycardia in clinical trials with fentanyl transdermal system was less than 1%.

CNS Effects

Central nervous system effects increase with increasing serum fentanyl concentrations.

INDICATIONS AND USAGE

Fentanyl transdermal system is indicated for management of persistent, moderate to severe chronic pain that:

- requires continuous, around-the-clock opioid administration for an extended period of time, and
- cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids

Fentanyl transdermal system should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to fentanyl transdermal system 25 mcg/hr (see DOSAGE AND ADMINISTRATION). Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60

mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could result, fentanyl transdermal system is contraindicated for use on an as needed basis (i.e., prn), for the management of post-operative or acute pain, or in patients who are not opioid-tolerant or who require opioid analgesia for a short period of time (see BOX WARNING and CONTRAINDICATIONS).

An evaluation of the appropriateness and adequacy of treating with immediate-release opioids is advisable prior to initiating therapy with any modified-release opioid. Prescribers should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen, to opioids, in a plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality, the Federation of State Medical Boards Model Policy, or the American Pain Society.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Patients receiving opioids should be routinely monitored for signs of misuse, abuse, and addiction. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

CONTRAINDICATIONS

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal system is contraindicated:

- in patients who are not opioid-tolerant
- in the management of acute pain or in patients who require opioid analgesia for a short period of time
- in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)
- in the management of mild pain
- in the management of intermittent pain (e.g., use on an as needed basis [prn])
- in situations of significant respiratory depression, especially in unmonitored settings where there is a lack of resuscitative equipment
- in patients who have acute or severe bronchial asthma

Fentanyl transdermal system is contraindicated in patients who have or are suspected of having paralytic ileus.

Fentanyl transdermal system is contraindicated in patients with known hypersensitivity to fentanyl or any component of this product.

WARNINGS

Fentanyl transdermal systems are intended for transdermal use (on intact skin) only. Using damaged or cut fentanyl transdermal systems can lead to the rapid release of the contents of the fentanyl transdermal system and absorption of a potentially fatal dose of fentanyl.

The safety of fentanyl transdermal system has not been established in children under 2 years of age. Fentanyl transdermal system should be administered to children only if they are opioid-tolerant and 2 years of age or older (see PRECAUTIONS - Pediatric Use).

Fentanyl transdermal system is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the fentanyl transdermal system dose when converting patients from another opioid medication can result in fatal overdose with the first dose. The mean elimination half-life of fentanyl transdermal system is 17 hours. Therefore, patients who have experienced serious adverse events, including overdose, will require monitoring for at least 24 hours after fentanyl transdermal system removal since serum fentanyl concentrations decline gradually and reach an approximate 50% reduction in serum concentrations 17 hours after system removal. Fentanyl transdermal system should be prescribed only by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for treatment of pain, and in the detection and management of hypoventilation including the use of opioid antagonists.

All patients and their caregivers should be advised to avoid exposing the fentanyl transdermal system application site to direct external heat sources, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, and heated water beds, etc., while wearing the system. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death (see PRECAUTIONS - Patients with Fever/External Heat).

Death and other serious medical problems have occurred when people were accidentally exposed to fentanyl transdermal system.

Examples of accidental exposure include transfer of a fentanyl transdermal system from an adult's body to a child while hugging, accidental sitting on a patch and possible accidental exposure of a caregiver's skin to the medication in the patch while the caregiver was applying or removing the patch.

Placing fentanyl transdermal system in the mouth, chewing it, swallowing it, or using it in ways other than indicated may cause choking or overdose that could result in death.

Misuse, Abuse and Diversion of Opioids

Fentanyl is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Fentanyl can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing fentanyl transdermal system in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

Fentanyl transdermal system has been reported as being abused by other methods and routes of administration. These practices will result in uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS and DRUG ABUSE AND ADDICTION).

Concerns about abuse, addiction and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Health care professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Hypoventilation (Respiratory Depression)

Serious or life-threatening hypoventilation may occur at any time during the use of fentanyl transdermal system especially during the initial 24 to 72 hours following initiation of therapy and following increases in dose.

Because significant amounts of fentanyl are absorbed from the skin for 17 hours or more after the system is removed, hypoventilation may persist beyond the removal of fentanyl transdermal system. Consequently, patients with hypoventilation should be carefully observed for degree of sedation and their respiratory rate monitored until respiration has stabilized.

The use of concomitant CNS active drugs requires special patient care and observation.

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in fentanyl transdermal system.

Respiratory depression is more likely to occur in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the “sighing” pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

Fentanyl transdermal system should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of fentanyl transdermal system may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Chronic Pulmonary Disease

Because potent opioids can cause serious or life-threatening hypoventilation, fentanyl transdermal system should be administered with caution to patients with pre-existing medical conditions predisposing them to hypoventilation. In such patients, normal analgesic doses of opioids may further decrease respiratory drive to the point of respiratory failure.

Head Injuries and Increased Intracranial Pressure

Fentanyl transdermal system should not be used in patients who may be particularly susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. Fentanyl transdermal system should be used with caution in patients with brain tumors.

Interactions with Other CNS Depressants

The concomitant use of fentanyl transdermal system with other central nervous system depressants, including but not limited to other opioids, sedatives, hypnotics, tranquilizers (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants, and alcohol, may cause respiratory depression, hypotension, and profound sedation or potentially result in coma. When such combined therapy is contemplated, the dose of one or both agents should be significantly reduced.

Interactions with Alcohol and Drugs of Abuse

Fentanyl may be expected to have additive CNS depressant effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Interactions with CYP3A4 Inhibitors

The concomitant use of fentanyl transdermal system with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleanomycin, clarithromycin, nelfinavir, and nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving fentanyl transdermal system and potent CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted. (See BOX WARNING, CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS and DOSAGE AND ADMINISTRATION for further information.)

PRECAUTIONS

General

Fentanyl transdermal system should not be used to initiate opioid therapy in patients who are not opioid-tolerant. Children converting to fentanyl transdermal system should be opioid-tolerant and 2 years of age or older (see BOX WARNING.)

Patients, family members and caregivers should be instructed to keep patches (new and used) out of the reach of children and others for whom fentanyl transdermal system was not prescribed. A considerable amount of active fentanyl remains in fentanyl transdermal system even after use as directed. Accidental or deliberate application or ingestion by a child or adolescent will cause respiratory depression that could result in death.

Cardiac Disease

Fentanyl may produce bradycardia. Fentanyl should be administered with caution to patients with bradyarrhythmias.

Hepatic or Renal Disease

Insufficient information exists to make recommendations regarding the use of fentanyl transdermal system in patients with impaired renal or hepatic function. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

Patients with Fever/External Heat

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one-third for patients with a body temperature of 40 °C (104 °F) due to temperature-dependent increases in fentanyl released from the system and increased skin permeability. Therefore, patients wearing fentanyl transdermal systems who develop fever should be monitored for opioid side effects and the fentanyl transdermal system dose should be adjusted if necessary.

All patients and their caregivers should be advised to avoid exposing the fentanyl transdermal system application site to direct external heat sources, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, and heated water beds, etc., while wearing the system. There is a potential for temperature-dependent increases in fentanyl release from the system.

Use in Pancreatic/Biliary Tract Disease

Fentanyl transdermal system may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like fentanyl transdermal system may cause increases in the serum amylase concentration.

Tolerance

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical Dependence

Physical dependence is a state of adaptation that is manifested by an opioid specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. In general, opioids should not be abruptly discontinued (see DOSAGE AND ADMINISTRATION: Discontinuation of Fentanyl Transdermal System).

Ambulatory Patients

Strong opioid analgesics impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving a car or operating machinery. Patients who have been given fentanyl transdermal system should not drive or operate dangerous machinery unless they are tolerant to the effects of the drug.

Information for Patients

A patient information sheet is included in the package of fentanyl transdermal systems dispensed to the patient.

Patients receiving fentanyl transdermal systems should be given the following instructions by the physician:

1. Patients should be advised that fentanyl transdermal systems contain fentanyl, an opioid pain medicine similar to morphine, hydromorphone, methadone, oxycodone, and oxymorphone.
2. Patients should be advised that each fentanyl transdermal system may be worn continuously for 72 hours, and that each patch should be applied to a different skin site after removal of the previous transdermal patch.
3. Patients should be advised that fentanyl transdermal systems should be applied to intact, non-irritated, and non-irradiated skin on a flat surface such as the chest, back, flank, or upper arm. Additionally, patients should be advised of the following:

- In young children or persons with cognitive impairment, the patch should be put on the upper back to lower the chances that the patch will be removed and placed in the mouth.
 - Hair at the application site should be clipped (not shaved) prior to patch application.
 - If the site of fentanyl transdermal system application must be cleansed prior to application of the patch, do so with clear water.
 - Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics.
 - Allow the skin to dry completely prior to patch application.
4. Patients should be advised that fentanyl transdermal system should be applied immediately upon removal from the sealed package and after removal of the protective liner. Additionally the patient should be advised of the following:
 - The fentanyl transdermal system should not be used if the seal is broken, or if it is altered, cut, or damaged in any way prior to application. This could lead to the rapid release of the contents of the fentanyl transdermal system and absorption of a potentially fatal dose of fentanyl. The transdermal patch should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges.
 - The patch should not be folded so that only part of the patch is exposed.
 5. Patients should be advised that while wearing the patch, they should avoid exposing the fentanyl transdermal system application site to direct external heat sources, such as:
 - heating pads,
 - electric blankets,
 - heat lamps,
 - saunas,
 - hot tubs, and
 - heated water beds, etc.,
 6. Patients should be advised that there is a potential for temperature-dependent increase in fentanyl release from the patch that could result in an overdose of fentanyl; therefore, if patients develop a high fever while wearing the patch they should contact their physician.
 7. Patients should be advised to fold (so that the adhesive side adheres to itself) and immediately flush down the toilet used fentanyl transdermal systems after removal from the skin.
 8. Patients should be instructed that, if the gel from the drug reservoir accidentally contacts the skin, the area should be washed clean with clear water and not soap, alcohol, or other chemicals, because these products may increase the ability of fentanyl to go through the skin.
 9. Patients should be advised that the dose of fentanyl transdermal system should NEVER be adjusted without the prescribing health care professional's instruction.
 10. Patients should be advised that fentanyl transdermal system may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).
 11. Patients should be advised to refrain from any potentially dangerous activity when starting on fentanyl transdermal system or when their dose is being adjusted, until it is established that they have not been adversely affected.
 12. Patients should be advised that fentanyl transdermal system should not be combined with alcohol or other CNS depressants (e.g., sleep medications, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.
 13. Patients should be advised to consult their physician or pharmacist if other medications are being or will be used with fentanyl transdermal system.
 14. Patients should be advised of the potential for severe constipation.
 15. Patients should be advised that if they have been receiving treatment with fentanyl transdermal system and cessation of therapy is indicated, it may be appropriate to taper the fentanyl transdermal system dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
 16. Patients should be advised that fentanyl transdermal system contains fentanyl, a drug with high potential for abuse.
 17. Patients, family members and caregivers should be advised to protect fentanyl transdermal system from theft or misuse in the work or home environment.

18. Patients should be advised that fentanyl transdermal system should never be given to anyone other than the individual for whom it was prescribed because of the risk of death or other serious medical problems to that person for whom it was not intended.
19. Patients should be instructed to keep fentanyl transdermal system in a secure place out of the reach of children due to the high risk of **fatal respiratory depression**.
20. When fentanyl transdermal system is no longer needed, the unused patches should be removed from their pouches, folded so that the adhesive side of the patch adheres to itself, and flushed down the toilet.
21. Women of childbearing potential who become, or are planning to become pregnant, should be advised to consult a physician prior to initiating or continuing therapy with fentanyl transdermal system.
22. Patients should be informed that accidental exposure or misuse may lead to death or other serious medical problems.
23. Patients should be informed that, if the patch dislodges and accidentally sticks to skin of another person, they should immediately take the patch off, wash the exposed area with water and seek medical attention for the accidentally exposed individual.

Drug Interactions

Agents Affecting Cytochrome P450 3A4 Isoenzyme System

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4), therefore potential interactions may occur when fentanyl transdermal system is given concurrently with agents that affect CYP3A4 activity. Coadministration with agents that induce 3A4 activity may reduce the efficacy of fentanyl transdermal system. The concomitant use of transdermal fentanyl with ritonavir or other potent 3A4 inhibitors such as ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazadone may result in an increase in fentanyl plasma concentrations (see BOX WARNING, CLINICAL PHARMACOLOGY - Drug Interactions, WARNINGS, and DOSAGE AND ADMINISTRATION). The concomitant use of other CYP3A4 inhibitors such as diltiazem and erythromycin with transdermal fentanyl may also result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate.

Central Nervous System Depressants

The concomitant use of fentanyl transdermal system with other central nervous system depressants, including but not limited to other opioids, sedatives, hypnotics, tranquilizers (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants, and alcohol, may cause respiratory depression, hypotension, and profound sedation, or potentially result in coma or death. When such combined therapy is contemplated, the dose of one or both agents should be significantly reduced.

MAO Inhibitors

Fentanyl transdermal system is not recommended for use in patients who have received MAOI within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals to evaluate the carcinogenic potential of fentanyl HCl have not been conducted. There was no evidence of mutagenicity in the Ames Salmonellamutagenicity assay, the primary rat hepatocyte unscheduled DNA synthesis assay, the BALB/c 3T3 transformation test, and the human lymphocyte and CHO chromosomal aberration *in-vitro* assays.

The potential effects of fentanyl on male and female fertility were examined in the rat model via two separate experiments. In the male fertility study, male rats were treated with fentanyl (0, 0.025, 0.1 or 0.4 mg/kg/day) via continuous intravenous infusion for 28 days prior to mating; female rats were not treated. In the female fertility study, female rats were treated with fentanyl (0, 0.025, 0.1 or 0.4 mg/kg/day) via continuous intravenous infusion for 14 days prior to mating until day 16 of pregnancy; male rats were not treated.

Analysis of fertility parameters in both studies indicated that an intravenous dose of fentanyl up to 0.4 mg/kg/day to either the male or the female alone produced no effects on fertility (this dose is approximately 1.6 times the daily human dose administered by a 100 mcg/hr patch on a mg/m² basis). In a separate study, a single daily bolus dose of fentanyl was shown to impair fertility in rats when given in intravenous doses of 0.3 times the human dose for a period of 12 days.

Pregnancy

Pregnancy Category C

No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

The potential effects of fentanyl on embryo-fetal development were studied in the rat, mouse, and rabbit models. Published literature reports that administration of fentanyl (0, 10, 100, or 500 mcg/kg/day) to pregnant female Sprague-Dawley rats from day 7 to 21 via implanted microosmotic minipumps did not produce any evidence of teratogenicity (the high dose is approximately 2 times the daily human dose administered by a 100 mcg/hr patch on a mg/m² basis). In contrast, the intravenous administration of fentanyl (0, 0.01, or 0.03 mg/kg) to bred female rats from gestation day 6 to 18 suggested evidence of embryotoxicity and a slight increase in mean delivery time in the 0.03 mg/kg/day group. There was no clear evidence of teratogenicity noted.

Pregnant female New Zealand White rabbits were treated with fentanyl (0, 0.025, 0.1, 0.4 mg/kg) via intravenous infusion from day 6 to day 18 of pregnancy. Fentanyl produced a slight decrease in the body weight of the live fetuses at the high dose, which may be attributed to maternal toxicity. Under the conditions of the assay, there was no evidence for fentanyl induced adverse effects on embryo-fetal development at doses up to 0.4 mg/kg (approximately 3 times the daily human dose administered by a 100 mcg/hr patch on a mg/m² basis).

There are no adequate and well-controlled studies in pregnant women. Fentanyl transdermal system should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures characteristic of neonatal abstinence syndrome in newborn infants. Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

The potential effects of fentanyl on prenatal and postnatal development were examined in the rat model. Female Wistar rats were treated with 0, 0.025, 0.1, or 0.4 mg/kg/day fentanyl via intravenous infusion from Day 6 of pregnancy through 3 weeks of lactation. Fentanyl treatment (0.4 mg/kg/day) significantly decreased body weight in male and female pups and also decreased survival in pups at Day 4. Both the mid-dose and high-dose of fentanyl animals demonstrated alterations in some physical landmarks of development (delayed incisor eruption and eye opening) and transient behavioral development (decreased locomotor activity at Day 28 which recovered by Day 50). The mid-dose and the high-dose are 0.4 and 1.6 times the daily human dose administered by a 100 mcg/hr patch on a mg/m² basis.

Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore, fentanyl transdermal system is not recommended for analgesia during labor and delivery.

Nursing Mothers

Fentanyl is excreted in human milk; therefore fentanyl transdermal system is not recommended for use in nursing women because of the possibility of effects in their infants.

Pediatric Use

The safety of fentanyl transdermal system was evaluated in three open-label trials in 291 pediatric patients with chronic pain, 2 years of age through 18 years of age. Starting doses of 25 mcg/hr and higher were used by 181 patients who had been on prior daily opioid doses of at least 45 mg/day of oral morphine or an equianalgesic dose of another opioid. Initiation of fentanyl transdermal system therapy in pediatric patients taking less than 60 mg/day of oral morphine or an equianalgesic dose of another opioid has not been evaluated in controlled clinical trials. Approximately 90% of the total daily opioid requirement (fentanyl transdermal system plus rescue medication) was provided by fentanyl transdermal system.

Fentanyl transdermal system was not studied in children under 2 years of age.

Fentanyl transdermal system should be administered to children only if they are opioid-tolerant and 2 years of age or older (see DOSAGE AND ADMINISTRATION and BOX WARNING).

To guard against accidental ingestion by children, use caution when choosing the application site for fentanyl transdermal system (see DOSAGE AND ADMINISTRATION) and monitor adhesion of the system closely.

Geriatric Use

Information from a pilot study of the pharmacokinetics of IV fentanyl in geriatric patients (N=4) indicates that the clearance of fentanyl may be greatly decreased in the population above the age of 60. The relevance of these findings to fentanyl transdermal system is unknown at this time.

Since elderly, cachectic, or debilitated patients may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance, they should not be started on fentanyl transdermal system doses higher than 25 mcg/hr unless they are already tolerating an around-the-clock opioid at a dose and potency comparable to fentanyl transdermal system-25 mcg/hr (see DOSAGE AND ADMINISTRATION).

Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

ADVERSE REACTIONS

In post-marketing experience, deaths from hypoventilation due to inappropriate use of fentanyl transdermal system have been reported (see BOX WARNING and CONTRAINDICATIONS).

Pre-Marketing Clinical Trial Experience:

Although fentanyl transdermal system use in post-operative or acute pain and in patients who are not opioid-tolerant is CONTRAINDICATED, the safety of fentanyl transdermal system was originally evaluated in 357 post-operative adult patients for 1 to 3 days and 153 cancer patients for a total of 510 patients. The duration of fentanyl transdermal system use varied in cancer patients; 56% of patients used fentanyl transdermal system for over 30 days, 28% continued treatment for more than 4 months, and 10% used fentanyl transdermal system for more than 1 year.

Hypoventilation was the most serious adverse reaction observed in 13 (4%) post-operative patients and in 3 (2%) of the cancer patients. Hypotension and hypertension were observed in 11 (3%) and 4 (1%) of the opioid-naïve patients.

Various adverse events were reported; a causal relationship to fentanyl transdermal system was not always determined. The frequencies presented here reflect the actual frequency of each adverse effect in patients who received fentanyl transdermal system. There has been no attempt to correct for a placebo effect, concomitant use of other opioids, or to subtract the frequencies reported by placebo-treated patients in controlled trials.

Adverse reactions reported in 153 cancer patients at a frequency of 1% or greater are presented in Table 1; similar reactions were seen in the 357 post-operative patients studied.

In the pediatric population, the safety of fentanyl transdermal system has been evaluated in 291 patients with chronic pain 2 to 18 years of age. The duration of fentanyl transdermal system use varied; 20% of pediatric patients were treated for ≤15 days; 46% for 16 to 30 days; 16% for 31 to 60 days; and 17% for at least 61 days. Twenty-five patients were treated with fentanyl transdermal system for at least 4 months and 9 patients for more than 9 months.

There was no apparent pediatric-specific risk associated with fentanyl transdermal system use in children as young as 2 years old when used as directed. The most common adverse events were fever (35%), vomiting (33%), and nausea (24%).

Adverse events reported in pediatric patients at a rate of ≥1% are presented in Table 1.

TABLE 1: ADVERSE EVENTS (at rate of ≥1%) Adult (N=380) and Pediatric (N=291) Clinical Trial Experience

Body System	Adults	Pediatrics
Body as a Whole	Abdominal pain*, headache*, fatigue*, back pain, fever, influenza-like symptoms*, accidental injury, rigors	Pain*, headache*, fever, syncope, abdominal pain, allergic reaction, flushing
Cardiovascular	Arrhythmia, chest pain	Hypertension, tachycardia
Digestive	Nausea**, vomiting**, constipation**, dry mouth**, anorexia*, diarrhea*, dyspepsia*, flatulence	Nausea**, vomiting**, constipation*, dry mouth, diarrhea
Nervous	Somnolence**, insomnia, confusion**, asthenia**, dizziness*, nervousness*, hallucinations*, anxiety*, depression*, euphoria*, tremor, abnormal coordination, speech disorder, abnormal thinking, abnormal gait, abnormal dreams, agitation, paresthesia, amnesia, syncope, paranoid reaction	Somnolence*, nervousness*, insomnia*, asthenia*, hallucinations, anxiety, depression, convulsions, dizziness, tremor, speech disorder, agitation, stupor, confusion, paranoid reaction
Respiratory	Dyspnea*, hypoventilation*, apnea*, hemoptysis, pharyngitis*, hiccups, bronchitis, rhinitis, sinusitis, upper respiratory tract infection*	Dyspnea, respiratory depression, rhinitis, coughing
Skin and Appendages	Sweating**, pruritus*, rash, application site reaction – erythema, papules, itching, edema	Pruritus*, application site reaction*, sweating increased, rash, rash erythematous, skin reaction localized
Urogenital	Urinary retention* Micturition disorder	Urinary retention

*Reactions occurring in 3% to 10% of fentanyl transdermal system patients

**Reactions occurring in 10% or more of fentanyl transdermal system patients

The following adverse effects have been reported in less than 1% of the 510 adult post-operative and cancer patients studied:

Cardiovascular: bradycardia

Digestive: abdominal distention

Nervous: aphasia, hypertonia, vertigo, stupor, hypotonia, depersonalization, hostility

Respiratory: stertorous breathing, asthma, respiratory disorder

Skin and Appendages, General: exfoliative dermatitis, pustules

Special Senses: amblyopia

Urogenital: bladder pain, oliguria, urinary frequency

Post-Marketing Experience – Adults:

The following adverse reactions have been reported in association with the use of fentanyl transdermal system and not reported in the pre-marketing adverse reactions section above:

Body as a Whole: edema

Cardiovascular: tachycardia

Metabolic and Nutritional: weight loss

Special Senses: blurred vision

Urogenital: decreased libido, anorgasmia, ejaculatory difficulty

DRUG ABUSE AND DEPENDENCE

Fentanyl transdermal system contains a high concentration of fentanyl, a potent Schedule II opioid agonist. Schedule II opioid substances, which include hydromorphone, methadone, morphine, oxycodone, and oxymorphone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression. Fentanyl, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

The high content of fentanyl in the patches (fentanyl transdermal system) may be a particular target for abuse and diversion. Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

“Drug seeking” behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Since fentanyl transdermal system may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Fentanyl transdermal systems are intended for transdermal use (to be applied on the skin) only. Using cut or damaged fentanyl transdermal systems or its contents can lead to the rapid release and absorption of a potentially fatal dose of fentanyl.

OVERDOSAGE**Clinical Presentation**

The manifestations of fentanyl overdosage are an extension of its pharmacologic actions with the most serious significant effect being hypoventilation.

Treatment

For the management of hypoventilation, immediate countermeasures include removing the fentanyl transdermal system and physically or verbally stimulating the patient. These actions can be followed by administration of a specific narcotic antagonist such as naloxone.

The duration of hypoventilation following an overdose may be longer than the effects of the narcotic antagonist’s action (the half-life of naloxone ranges from 30 to 81 minutes). The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after system removal; repeated administration of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and the release of catecholamines.

Always ensure a patent airway is established and maintained, administer oxygen and assist or control respiration as indicated and use an oropharyngeal airway or endotracheal tube if necessary. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy.

DOSAGE AND ADMINISTRATION**Special Precautions**

Fentanyl transdermal system contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (fentanyl transdermal system) may be a particular target for abuse and diversion.

Fentanyl transdermal systems are intended for transdermal use (on intact skin) only. Using damaged fentanyl transdermal systems can lead to the rapid release and absorption of a potentially fatal dose of fentanyl. In addition, exposure to the contents of a fentanyl transdermal system can lead to potentially fatal respiratory depression.

Fentanyl transdermal system is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the fentanyl transdermal system dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of fentanyl transdermal system, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

The concomitant use of fentanyl transdermal system with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving fentanyl transdermal system and potent CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted. (See BOX WARNING, WARNINGS, CLINICAL PHARMACOLOGY—Drug Interactions and PRECAUTIONS for further information.)

General Principles

Fentanyl transdermal system is indicated for management of **persistent**, moderate to severe chronic pain that:

- requires continuous, around-the-clock opioid administration for an extended period of time
- cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids

Fentanyl transdermal system should **ONLY** be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to fentanyl transdermal system 25 mcg/hr. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg oral hydromorphone daily, or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal system is contraindicated:

- in patients who are not opioid-tolerant
- in the management of acute pain or in patients who require opioid analgesia for a short period of time
- in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)
- in the management of mild pain
- in the management of intermittent pain (e.g., use on an as needed basis [prn])

(See CONTRAINDICATIONS for further information.)

Safety of fentanyl transdermal system has not been established in children under 2 years of age. Fentanyl transdermal system should be administered to children only if they are opioid-tolerant and 2 years of age or older (see PRECAUTIONS - Pediatric Use).

Prescribers should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality, the Federation of State Medical Boards Model Policy, or the American Pain Society.

With all opioids, the safety of patients using the products is dependent on health care practitioners prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

As with all opioids, dosage should be individualized. The most important factor to be considered in determining the appropriate dose is the extent of pre-existing opioid-tolerance (see BOX WARNING and CONTRAINDICATIONS). Initial doses should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Fentanyl transdermal system should be applied to intact, non-irritated, and non-irradiated skin on a flat surface such as the chest, back, flank, or upper arm. In young children and persons with cognitive impairment, adhesion should be monitored and the upper back is the preferred location to minimize the potential of inappropriate patch removal. Hair at the application site should be clipped (not shaved) prior to system application. If the site of fentanyl transdermal system application must be cleansed prior to application of the patch, do so with clear water. Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics. Allow the skin to dry completely prior to patch application.

Fentanyl transdermal system should be applied immediately upon removal from the sealed package. Do not use if the seal is broken. Do not alter the patch (e.g., cut) in any way prior to application and do not use cut or damaged patches.

The transdermal system should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges. If the gel from the drug reservoir accidentally contacts the skin of the patient or caregiver, the skin should be washed with copious amounts of water. Do not use soap, alcohol, or other solvents to remove the gel because they may enhance the drug's ability to penetrate the skin.

Each fentanyl transdermal system may be worn continuously for 72 hours. The next patch should be applied to a different skin site after removal of the previous transdermal system.

Fentanyl transdermal system should be kept out of the reach of children. Used patches should be folded so that the adhesive side of the patch adheres to itself, then the patch should be flushed down the toilet immediately upon removal. Patients should dispose of any patches remaining from a prescription as soon as they are no longer needed. Unused patches should be removed from their pouches, folded so that the adhesive side of the patch adheres to itself, and flushed down the toilet.

Dose Selection

Doses must be individualized based upon the status of each patient and should be assessed at regular intervals after fentanyl transdermal system application. Reduced doses of fentanyl transdermal system are suggested for the elderly and other groups discussed in PRECAUTIONS.

Fentanyl transdermal system is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression.

Pediatric patients converting to fentanyl transdermal system therapy with a 25 mcg/hr patch should be opioid-tolerant and receiving at least 60 mg oral morphine equivalents per day. The dose conversion schedule described in Table C and method of titration described below are recommended in opioid-tolerant pediatric patients over 2 years of age with chronic pain (see PRECAUTIONS - Pediatric Use).

In selecting an initial fentanyl transdermal system dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (e.g., whether it is a pure agonist or mixed agonist-antagonist); 2) the reliability of the relative potency estimates used to calculate the fentanyl transdermal system dose needed (potency estimates may vary with the route of administration); 3) the degree of opioid tolerance; and 4) the general condition and medical status of the patient. Each patient should be maintained at the lowest dose providing acceptable pain control.

Initial Fentanyl Transdermal System Dose Selection

Overestimating the fentanyl transdermal system dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of fentanyl transdermal system, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

There has been no systematic evaluation of fentanyl transdermal system as an initial opioid analgesic in the management of chronic pain, since most patients in the clinical trials were converted to fentanyl transdermal system from other narcotics. In addition, patients who are not opioid-tolerant have experienced hypoventilation and death during use of fentanyl transdermal system. Therefore, fentanyl transdermal system should be used only in patients who are opioid-tolerant.

To convert patients from oral or parenteral opioids to fentanyl transdermal system, use Table C:

Alternatively, for adult and pediatric patients taking opioids or doses not listed in Table C, use the following methodology:

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using Table D.
3. Table E displays the range of 24-hour oral morphine doses that are recommended for conversion to each fentanyl transdermal system dose. Use this table to find the calculated 24-hour morphine dose and the corresponding fentanyl transdermal system dose. Initiate fentanyl transdermal system treatment using the recommended dose and titrate patients upwards (no more frequently than every 3 days after the initial dose or than every 6 days thereafter) until analgesic efficacy is attained. The recommended starting dose when converting from other opioids to fentanyl transdermal system is likely too low for 50% of patients. This starting dose is recommended to minimize the potential for overdosing patients with the first dose. For delivery rates in excess of 100 mcg/hr, multiple systems may be used.

TABLE C¹ DOSE CONVERSION GUIDELINES

Current Analgesic	Daily Dosage (mg/d)			
Oral morphine	60–134	135–224	225–314	315–404
IM/IV morphine	10–22	23–37	38–52	53–67
Oral oxycodone	30–67	67.5–112	112.5–157	157.5–202
IM/IV oxycodone	15–33	33.1–56	56.1–78	78.1–101
Oral codeine	150–447	448–747	748–1047	1048–1347
Oral hydromorphone	8–17	17.1–28	28.1–39	39.1–51
IV hydromorphone	1.5–3.4	3.5–5.6	5.7–7.9	8–10
IM meperidine	75–165	166–278	279–390	391–503
Oral methadone	20–44	45–74	75–104	105–134
IM methadone	10–22	23–37	38–52	53–67
	⇓	⇓	⇓	⇓

Recommended Fentanyl Transdermal System Dose	25 mcg/hr	50 mcg/hr	75 mcg/hr	100 mcg/hr
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Alternatively, for adult and pediatric patients taking opioids or doses not listed in Table C, use the conversion methodology outlined above with Table D.

¹Table C should not be used to convert from fentanyl transdermal system to other therapies because this conversion to fentanyl transdermal system is conservative. Use of Table C for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see DOSAGE AND ADMINISTRATION Discontinuation of Fentanyl Transdermal System).

TABLE D^{1,a} EQUIANALGESIC POTENCY CONVERSION

Name	IM ^{b,c}	Equianalgesic Dose (mg)	PO
Morphine	10		60 (30) ^d
Hydromorphone (Dilaudid®) ^e	1.5		7.5
Methadone (Dolophine®) ^f	10		20
Oxycodone	15		30
Levorphanol (Levo-Dromoran®) ^g	2		4
Oxymorphone (Numorphan®) ^h	1		10 (PR)
Meperidine (Demerol®) ⁱ	75		—
Codeine	130		200

¹Table D should not be used to convert from fentanyl transdermal system to other therapies because this conversion to fentanyl transdermal system is conservative. Use of Table D for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see DOSAGE AND ADMINISTRATION Discontinuation of Fentanyl Transdermal System).

^aAll IM and PO doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect. IM denotes intramuscular, PO oral, and PR rectal.

^bBased on single-dose studies in which an intramuscular dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from parenteral to an oral route. Reference: Foley, K.M. (1985) The treatment of cancer pain. NEJM 313(2):84-95.

^cAlthough controlled studies are not available, in clinical practice it is customary to consider the doses of opioid given IM, IV or subcutaneously to be equivalent. There may be some differences in pharmacokinetic parameters such as C_{max} and T_{max}.

^dThe conversion ratio of 10 mg parenteral morphine = 30 mg oral morphine is based on clinical experience in patients with chronic pain. The conversion ratio of 10 mg parenteral morphine = 60 mg oral morphine is based on a potency study in acute pain. Reference: Ashburn and Lipman (1993) Management of pain in the cancer patient. Anesth Analg 76:402-416.

^eDilaudid® is a registered trademark of Abbott Laboratories.

^fDolophine® is a registered trademark of Roxane Laboratories.

^gLevo-Dromoran® is a registered trademark of Valeant Pharmaceuticals, International.

^hNumorphan® is a registered trademark of Endo Pharmaceuticals, Inc.

ⁱDemerol® is a registered trademark of Sanofi-Synthelabo, Inc.

TABLE E1 RECOMMENDED INITIAL FENTANYL TRANSDERMAL SYSTEM DOSE BASED UPON DAILY ORAL MORPHINE DOSE

Oral 24-hour Morphine (mg/day)	Fentanyl Transdermal System Dose (mcg/hr)
60–134 ²	25
135–224	50
225–314	75
315–404	100

405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1034	275
1035–1124	300

NOTE: In clinical trials, these ranges of daily oral morphine doses were used as a basis for conversion to fentanyl transdermal system.

¹Table E should not be used to convert from fentanyl transdermal system to other therapies because this conversion to fentanyl transdermal system is conservative. Use of Table E for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see DOSAGE AND ADMINISTRATION - Discontinuation of Fentanyl Transdermal System).

²Pediatric patients initiating therapy on a 25 mcg/hr fentanyl transdermal system should be opioid-tolerant and receiving at least 60 mg oral morphine equivalents per day.

The majority of patients are adequately maintained with fentanyl transdermal system administered every 72 hours. Some patients may not achieve adequate analgesia using this dosing interval and may require systems to be applied every 48 hours rather than every 72 hours. An increase in the fentanyl transdermal system dose should be evaluated before changing dosing intervals in order to maintain patients on a 72-hour regimen. Dosing intervals less than every 72 hours were not studied in children and adolescents and are not recommended.

Because of the increase in serum fentanyl concentration over the first 24 hours following initial system application, the initial evaluation of the maximum analgesic effect of fentanyl transdermal system cannot be made before 24 hours of wearing. The initial fentanyl transdermal system dosage may be increased after 3 days (see Dose Titration).

During the initial application of fentanyl transdermal system, patients should use short-acting analgesics as needed until analgesic efficacy with fentanyl transdermal system is attained. Thereafter, some patients still may require periodic supplemental doses of other short-acting analgesics for “breakthrough” pain.

Dose Titration

The recommended initial fentanyl transdermal system dose based upon the daily oral morphine dose is conservative, and 50% of patients are likely to require a dose increase after initial application of fentanyl transdermal system. The initial fentanyl transdermal system dosage may be increased after 3 days based on the daily dose of supplemental opioid analgesics required by the patient in the second or third day of the initial application.

Physicians are advised that it may take up to 6 days after increasing the dose of fentanyl transdermal system for the patient to reach equilibrium on the new dose (see graph in CLINICAL PHARMACOLOGY). Therefore, patients should wear a higher dose through two applications before any further increase in dosage is made on the basis of the average daily use of a supplemental analgesic.

Appropriate dosage increments should be based on the daily dose of supplementary opioids, using the ratio of 45 mg/24 hours of oral morphine to a 12.5 mcg/hr increase in fentanyl transdermal system dose.

Discontinuation of Fentanyl Transdermal System

To convert patients to another opioid, remove fentanyl transdermal system and titrate the dose of the new analgesic based upon the patient’s report of pain until adequate analgesia has been attained. Upon system removal, 17 hours or more are required for a 50% decrease in serum fentanyl concentrations. Opioid withdrawal symptoms (such as nausea, vomiting, diarrhea, anxiety, and shivering) are possible in some patients after conversion or dose adjustment. For patients requiring discontinuation of opioids, a gradual downward titration is recommended since it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

Tables C, D, and E should not be used to convert from fentanyl transdermal system to other therapies. Because the conversion to fentanyl transdermal system is conservative, use of Tables C, D, and E for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible.

HOW SUPPLIED

Fentanyl transdermal system is supplied in cartons containing 5 individually packaged systems. See chart for information regarding individual systems.

Fentanyl Transdermal System

Dose (mcg/hr)	System Size (cm ²)	Fentanyl Content (mg)	NDC Number
Fentanyl Transdermal System-25	10	2.5	67767-120-18
Fentanyl Transdermal System-50	20	5	67767-121-18
Fentanyl Transdermal System-75	30	7.5	67767-122-18
Fentanyl Transdermal System-100	40	10	67767-123-18

Safety and Handling

Fentanyl transdermal system is supplied in sealed transdermal systems which pose little risk of exposure to health care workers. If the gel from the drug reservoir accidentally contacts the skin, the area should be washed with copious amounts of water. Do not use soap, alcohol, or other solvents to remove the gel because they may enhance the drug's ability to penetrate the skin. Do not cut or damage fentanyl transdermal system. If the fentanyl transdermal system is cut or damaged, controlled drug delivery will not be possible, which can lead to the rapid release and absorption of a potentially fatal dose of fentanyl.

KEEP FENTANYL TRANSDERMAL SYSTEM OUT OF THE REACH OF CHILDREN AND PETS

Do not store above 77 °F (25 °C). Apply immediately after removal from individually sealed package. Do not use if the seal is broken. **For transdermal use only.**

Rx only

A Schedule CII Narcotic. DEA Order Form Required.

Distributed By:

Actavis South Atlantic LLC
Sunrise, FL 33325

Manufactured by:

Corium International, Inc.,
Grand Rapids, MI 49512
August 2007
CAW0369

Patient Information

FENTANYL TRANSDERMAL SYSTEM CII

This leaflet contains important information about fentanyl transdermal system. Read this Patient Information carefully before you start using fentanyl transdermal system. Read it each time you get a prescription. There may be new information.

This information does not take the place of talking to your health care provider about your medical condition or your treatment. Only your health care provider can decide if fentanyl transdermal system is the right treatment for you. If you do not understand some of this information or have questions, talk with your health care provider.

What is the most important information I should know about fentanyl transdermal system?

- Fentanyl transdermal system contains fentanyl, a strong opioid narcotic pain medicine. Fentanyl transdermal system can cause serious side effects, including trouble breathing, which can be fatal, especially if used the wrong way.
- Fentanyl transdermal system is only for patients with chronic (around the clock) pain that is moderate to severe and expected to last for weeks or longer. Fentanyl transdermal system should only be started if you are already using other opioid narcotic medicines
- Fentanyl transdermal system is not for patients who need opioid pain medicines for only a short time. This includes the pain that happens with surgery (such as tonsillectomies), medical, or dental procedures (such as wisdom tooth removal).
- Fentanyl transdermal system is not for occasional ("as needed") use.
- You should NOT use fentanyl transdermal system unless you are opioid tolerant. You are opioid tolerant if you have been taking at least 60 milligrams (mg) of oral morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equally strong dose of another opioid for a week or longer before starting fentanyl transdermal system. If you are unsure if you are opioid-tolerant, discuss this with your health care provider.
- Fentanyl transdermal system is only for adults and children 2 years of age or older who have already been using opioid narcotic pain medicines for a week or more. Children should ONLY use fentanyl transdermal system if they have been taking at least 60 milligrams (mg) of oral morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral

hydromorphone daily, or an equally strong dose of another opioid for a week or longer before starting fentanyl transdermal system.

- **Do not use the fentanyl transdermal system if the seal is broken or the patch is cut, damaged, or changed in any way.** Using a patch that is cut, damaged, or changed in any way can expose you to the contents of the patch, which contains a potentially fatal dose of medicine.
- **Keep fentanyl transdermal system in a safe place away from children.** Accidental use by a child is a medical emergency and can result in death. If a child accidentally is exposed to a **fentanyl transdermal system**, call your local Poison Control Center or the nearest emergency room right away.
- **Fentanyl transdermal system is an opioid (narcotic) pain medicine.** There is a chance you could get addicted to **fentanyl transdermal system**. The chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.
- Keep your **fentanyl transdermal system** in a safe place to protect it from being stolen since it can be a target for people who abuse narcotic medicines or street drugs. Never give **fentanyl transdermal system** to anyone else, even if they have the same symptoms you have. It may harm them and cause death. Selling or giving away this medicine is against the law.
- **Some medicines may cause serious or life-threatening side effects when used with fentanyl transdermal system. Talk to your health care provider about all the medicines you are taking.**

What is fentanyl transdermal system?

Fentanyl transdermal system is a prescription medicine that contains fentanyl. Fentanyl transdermal system is a federally controlled substance (CII) because it is a strong opioid narcotic pain medicine that can be abused by people who abuse prescription medicines or street drugs.

Fentanyl transdermal system is only for patients with chronic (around the clock) pain that is moderate to severe and expected to last for weeks or longer.

You should ONLY use fentanyl transdermal system if you have been taking at least 60 milligrams (mg) of oral morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equally strong dose of another opioid for a week or longer before starting fentanyl transdermal system.

Fentanyl transdermal system is not for patients who need opioid pain medicines for only a short time. This includes the pain that happens with surgery (such as tonsillectomies), medical, or dental procedures (such as wisdom tooth removal).

Fentanyl transdermal system is not for occasional (“as needed”) use.

Fentanyl transdermal system should not be the first opioid (narcotic) pain medicine that is prescribed for your pain.

Fentanyl transdermal system is only for opioid tolerant children 2 years of age or older who are already using other opioid narcotic pain medicines. Pediatric patients 2 years of age or older are opioid tolerant if they are taking at least 60 milligrams (mg) of oral morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equally strong dose of another opioid for a week or longer before starting fentanyl transdermal system.

Who should not use fentanyl transdermal system?

Do not use fentanyl transdermal system:

- **If you are NOT already using other opioid narcotic medicines**
- If you need opioid pain medicines for only a short time
- For pain from surgery, medical, or dental procedures
- If your pain can be taken care of by occasional use of other pain medicines
- In children who are less than 2 years of age
- In children 2 years of age or older who are not already using other opioid narcotic pain medicines (opioid tolerant)
- If you have acute (sudden) or severe asthma
- If you have gastrointestinal problem called paralytic ileus
- If you are allergic to any of the ingredients in fentanyl transdermal system

What should I tell my health care provider before starting fentanyl transdermal system?

- **trouble breathing or lung problems such as asthma, wheezing, or shortness of breath**

- **a head injury or brain problems**
- **a heart problem called bradycardia (slow heart beat)**
- **liver or kidney problems**
- seizures (convulsions or fits)
- gallbladder problems
- low thyroid (hypothyroidism)
- low blood pressure
- problems urinating
- major depression
- hallucinations (seeing or hearing things that are not seen by other people)
- adrenal gland problems such as Addison's disease
- a past or present drinking problem or alcoholism, or a family history of this problem
- a past or present drug abuse or addiction problem, or a family history of this problem
- **Have skin reactions to adhesives (glues) used in fentanyl transdermal system.** See the end of this leaflet for a complete list of all the ingredients in fentanyl transdermal system.

Tell your health care provider if you:

- **Are pregnant or planning to become pregnant.** Fentanyl transdermal system may harm your unborn baby.
- **Are breast feeding.** The medicine in fentanyl transdermal system passes into your milk and can harm your baby.

Some medicines may cause serious or life-threatening side effects when used with fentanyl transdermal system. Tell your health care provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. Sometimes, the doses of certain medicines and fentanyl transdermal system need to be changed when used together. Be especially careful about other medicines that make you sleepy such as other pain medicines, sleeping pills, anxiety medicines, antihistamines, or tranquilizers.

Do not start any new prescription medicine, non-prescription medicine, or herbal supplement while using fentanyl transdermal system until you have talked to your health care provider. Your health care provider will tell you if it is safe to take other medicines while you are using fentanyl transdermal system.

What should I know about using fentanyl transdermal system in children?

Fentanyl transdermal system can be used in children 2 years of age or older only if they are already using other opioid narcotic pain medicines for a week or more. Children should ONLY use fentanyl transdermal system if they have been taking at least 60 milligrams (mg) of oral morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equally strong dose of another opioid for a week or longer before starting fentanyl transdermal system.

When fentanyl transdermal system is used in young children; put the patch on the child's upper back. This will lower the chances that the child will remove the patch and put it in their mouth.

Keep fentanyl transdermal system in a safe place. Keep fentanyl transdermal system out of the reach of children. **Accidental use in children is a medical emergency and can result in death. If a child accidentally takes fentanyl transdermal system, call your local Poison Control Center or go to the nearest emergency room right away.**

How do I use fentanyl transdermal system?

- Follow your health care provider's directions exactly. Your health care provider may change your dose after seeing how the medicine affects you.
- **Do not use the fentanyl transdermal system if the seal is broken or the patch is cut, damaged, or changed in any way. Using a patch that is cut, damaged, or changed in any way can expose you to the contents of the patch, which contains a potentially fatal dose of the medicine.**

- Do not change your dose or stop using fentanyl transdermal system unless your health care provider tells you to. Do not use fentanyl transdermal system more often than prescribed. (See the end of this leaflet for “How and where to apply fentanyl transdermal system.”)
- Do not wear more than **one** fentanyl transdermal system at a time, unless your health care provider tells you to do so.
- Call your health care provider right away if you get a fever higher than 102 °F. A fever may cause too much of the medicine in fentanyl transdermal system to pass into your body. Your health care provider may tell you to use a lower dose while you have a fever.
- If you use more fentanyl transdermal system than your health care provider has prescribed or overdose, get emergency medical help right away.
- If you have concerns about abuse or addiction when using your pain medicine or if you have experienced drug or alcohol abuse or addiction in the past, or have a family history of these problems, talk to your health care provider.
- After you have stopped using a patch, be sure to fold the sticky sides of the patch together and flush it down the toilet. Do not put used fentanyl transdermal systems in a garbage can.
- If your health care provider tells you to stop using fentanyl transdermal system, throw away the unused packages. Open the unused packages and fold the sticky sides of the patches together, and flush them down the toilet. (See “What should I avoid while using fentanyl transdermal system”)

What should I avoid while using fentanyl transdermal system?

- **Do not use heat sources such as heating pads, electric blankets, heat lamps, saunas, hot tubs, or heated waterbeds. Do not take long hot baths or sun bathe.** All of these can make your temperature rise and cause too much of the medicine in fentanyl transdermal system to be released at once and this can be dangerous.
- **Do not drink any alcohol while using fentanyl transdermal system.** It can increase your chances of having dangerous side effects.
- **Do not drive, operate heavy machinery, or do other possibly dangerous activities** until you know how fentanyl transdermal system affects you. Fentanyl transdermal system can make you sleepy. Ask your health care provider to tell you when it is okay to do these activities.
- **Do not stop using fentanyl transdermal system suddenly.** Your body can develop a physical dependence on **fentanyl transdermal system**. If your health care provider decides you no longer need fentanyl transdermal system, ask how to slowly reduce this medicine so you don’t have withdrawal symptoms. **Do not stop taking fentanyl transdermal system without talking to your health care provider.** Stopping fentanyl transdermal system suddenly can make you sick with withdrawal symptoms.
- **Do not breast feed unless your health care provider tells you it is okay.** Fentanyl transdermal system passes into your milk and can cause serious problems for your baby.
- **Do not take other medicines without talking to your health care provider.** Other medicines include prescription and non-prescription medicines, vitamins, and herbal supplements. **Be especially careful about other medicines that make you sleepy.**

What are the possible side effects of fentanyl transdermal system?

- Fentanyl transdermal system can cause serious side effects, including trouble breathing, which can be fatal, especially if used the wrong way. See “What is the most important information I should know about fentanyl transdermal system?”

Call your health care provider right away or get emergency medical help if you:

- Have trouble breathing
- Have extreme drowsiness with slowed breathing
- Have shortness of breath (little chest movement with breathing)
- Feel faint, dizzy, confused, or have other unusual symptoms

These can be symptoms that you have taken too much (overdose) fentanyl transdermal system or the dose is too high for you. These symptoms may lead to serious problems or death if not treated right away.

Some medicines may cause serious or life-threatening side effects when used with fentanyl transdermal system. Talk to your health care provider about all the medicines you are taking.

You can develop physical dependence on fentanyl transdermal system. Stopping fentanyl transdermal system suddenly can make you sick with withdrawal symptoms. Talk to your health care provider about slowly stopping fentanyl transdermal system.

There is a chance you could get addicted to fentanyl transdermal system. The chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.

Fentanyl transdermal system can cause your blood pressure to drop. This can make you feel dizzy if you get up too fast from sitting or lying down.

The common side effects with fentanyl transdermal system are nausea, vomiting, constipation, dry mouth, sleepiness, confusion, weakness, and sweating. Although uncommon, trouble sleeping and seizures were reported in children. These are not all the possible side effects of fentanyl transdermal system. For a complete list, ask your health care provider or pharmacist.

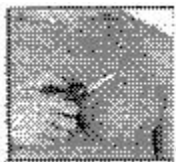
Constipation (less frequent than usual or hard bowel movements) is a very common side effect of opioids including fentanyl transdermal system and is unlikely to go away without treatment. Talk to your health care provider about the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking fentanyl transdermal system.

- Talk to your health care provider about any side effect that concerns you.

How and where to apply fentanyl transdermal system

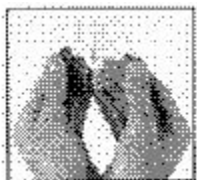
In the hospital, your health care provider or other medical person will apply fentanyl transdermal system for you. At home, you or a member of your family may apply fentanyl transdermal system to your skin. You need to check the patches often to make sure that they are sticking well to the skin. In young children and people who have impaired thinking, put the patch on the upper back. This will lower the chances that the patch will be removed.

1. Prepare:



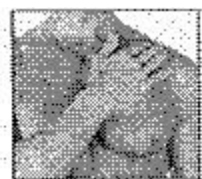
For adults, put the patch on the chest, back, flank (sides of the waist), or upper arm in a place where there is no hair. Put it on right away after you have removed it from the pouch and after you have removed the protective liner. Avoid sensitive areas or those that move around a lot. If there is hair, **do not shave (shaving irritates the skin)**. Instead, clip hair as close to the skin as possible. Clean the skin area with clear water **only**. **Pat skin completely dry.** Do not use anything on the skin (soaps, lotions, oils, alcohol, etc.) before the patch is applied.

2. Peel:



Peel the liner from the back of the patch and throw away. **Touch the sticky side as little as possible.**

3. Press:



Press the patch onto the skin **with the palm of your hand and hold there for a minimum of 30 seconds**. Make sure it sticks well, especially at the edges.

- Each fentanyl transdermal system is sealed in its own protective pouch. Do not remove the fentanyl transdermal system from the pouch until you are ready to use it. When you are ready to put on fentanyl transdermal system, tear open the pouch along the dotted line, starting at the slit, and remove the fentanyl transdermal system.
- Do not put the fentanyl transdermal system on skin that is very oily, burned, broken out, cut, irritated, or damaged in any way.
- If you have any questions about where on your body you should or should not apply the patch, please ask your health care provider.
- Fentanyl transdermal system may not stick to all patients. If the patch does not stick well or comes loose after applying, tape the edges down with first aid tape. If the patch falls off, throw it away and put a new one on at a different skin site (see “Disposing of fentanyl transdermal system”).

- Wash your hands when you have finished applying fentanyl transdermal system.
- Remove fentanyl transdermal system after wearing it for 3 days (see “Disposing of fentanyl transdermal system”). Choose a *different* place on the skin to apply a new fentanyl transdermal system and repeat Steps 1 through 3. **Do not apply the new patch to the same place as the last one.**

When to apply fentanyl transdermal system?

- You can apply fentanyl transdermal system at any time of the day. Change it at about the same time of day 3 days later or as directed by your health care provider.
- Do not apply the new fentanyl transdermal system to the same place where you removed the last fentanyl transdermal system.
- Your health care provider may increase your fentanyl transdermal system dose if your pain is not controlled well. **If you continue to have pain, call your health care provider.**

Water and fentanyl transdermal system

You can bathe, swim or shower while you are wearing fentanyl transdermal system. If the patch falls off, put a new fentanyl transdermal system on your skin. Make sure the new skin area you have chosen is dry before putting on a new fentanyl transdermal system.

Disposing of fentanyl transdermal system

- Before putting on a new fentanyl transdermal system, remove the patch you have been wearing.
- Fold the used fentanyl transdermal system in half so that the sticky side sticks to itself. **Flush the used fentanyl transdermal system down the toilet right away. A used fentanyl transdermal system may be dangerous for or even lead to death in babies, children, pets, and adults who have not been prescribed fentanyl transdermal system.**
- Throw away any fentanyl transdermal systems that are left over from your prescription as soon as they are no longer needed. Remove the leftover patches from their protective pouch and remove the protective liner. **Fold the patches in half with the sticky sides together, and flush the patches down the toilet.** Do not flush the pouch or the protective liner down the toilet. These items can be thrown away in a garbage can.

Safety and handling of fentanyl transdermal system

Fentanyl transdermal system is a patch with a drug-containing gel sealed inside. This design keeps the gel from getting on your hands or body. If the gel from the drug reservoir accidentally contacts the skin, the area should be washed with large amounts of water. Do not use soap, alcohol, or other solvents to remove the gel because they may increase the drug’s ability to go through the skin.

Do not use the fentanyl transdermal system if the seal is broken or the patch is cut, damaged, or changed in any way. Using a patch that is cut, damaged, or changed in any way can expose you to the contents of the patch, which contains potentially fatal dose of medicine.

The patch must be used only on the skin of the person for whom it was prescribed. If the patch comes off and accidentally sticks to the skin of another person, take the patch off of that person right away, wash the area with water, and seek immediate medical attention. Call a health care provider or poison control center.

Prevent theft and misuse. Fentanyl transdermal system contains an opioid narcotic pain medicine that can be a target for people who abuse prescription medicines. Keep your fentanyl transdermal system in a safe place, to protect it from theft. Never give fentanyl transdermal system to anyone else because it may be dangerous to them. Selling or giving away this medicine is against the law.

How should fentanyl transdermal system be stored?

Store fentanyl transdermal system below 77 °F (25 °C). Remember, the inside of your car can reach temperatures much higher than this in the summer.

Keep fentanyl transdermal system in its protective pouch until you are ready to use it.

Keep fentanyl transdermal system in a safe place. Keep fentanyl transdermal system out of the reach of children. **Accidental use in children is a medical emergency and can result in death. If a child accidentally takes fentanyl transdermal system, call your local Poison Control Center or get emergency medical help right away.**

General information about the safe and effective use of fentanyl transdermal system

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use fentanyl transdermal system for a condition for which it was not prescribed. Do not give fentanyl transdermal system to other people, even if they have the same symptoms you have. **Fentanyl transdermal system can harm other people and even cause death. Sharing fentanyl transdermal system is against the law.**

Keep fentanyl transdermal system out of the reach of children and pets. Accidental use in children and pets is a medical emergency and can result in death. If a child or pet accidentally take fentanyl transdermal system, call your local Poison Control Center or get emergency medical help right away.

This leaflet summarizes the most important information about fentanyl transdermal system. If you would like more information, talk with your health care provider. You can ask your health care provider or pharmacist for information about fentanyl transdermal system that is written for health professionals.

For questions about fentanyl transdermal system, call Actavis at 1-877-422-7452 or visit our website at www.actavis.us.

This patient information has been approved by the United States Food and Drug Administration.

What are the ingredients of fentanyl transdermal system?

Active Ingredient: fentanyl

Inactive Ingredients: alcohol*, ethylene-vinyl acetate copolymer membrane, hydroxyethyl cellulose, polyester film backing, silicone adhesive.

*Less than 0.2 mL of alcohol is released from the patch during use.

Rx ONLY

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Sunrise, FL 33325

Manufactured by:

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Grand Rapids, MI 49512

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